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Sponsor: Sanofi **Drug substance(s):** SAR441255	**Study Identifiers:** U1111-1210-0180, NCT04521738 **Study code**: TDU15478

Title of the study: A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending and multiple ascending subcutaneous doses of SAR441255 in lean to overweight (SAD part) and overweight to obese adult subjects (MAD part)

This document reports the single ascending subcutaneous dose part of the study (TDU15478)

Study center: 1 center in the USA.

Study period:

Date first subject enrolled: 25/Apr/2019

Date last subject last visit: 26/Sep/2019

Study Status: The study was definitely and prematurely stopped due to the Sponsor's decision which was not related to any safety issue.

Phase of development: Phase 1

Objectives:

- Primary objective:
  - The safety and tolerability of SAR441255 after single ascending subcutaneous (SC) doses in lean-to-overweight, otherwise healthy adult subjects.
- Secondary objectives:
  - The pharmacokinetic (PK) parameters of SAR441255 in plasma after single ascending SC doses.
  - The pharmacodynamic (PD) effects on glycemic parameters (fasting and postprandial glucose, C-peptide and insulin).

Methodology:

Phase 1, single-center; 2-part, double-blind, randomized, placebo-controlled study in lean-to-overweight (single ascending dose [SAD] with starting dose of 3 µg) adult subjects.

There were 3 protocol amendments in this study. Amended protocol 1 was issued prior to the inclusion of any subject. Amended protocols 2 and 3 were instituted after the first subject was enrolled.

Number of subjects:

Planned: 56 (depending on the number of cohorts)

Randomized: 48

Treated: 48

Evaluated:

Pharmacodynamic: 48

Safety: 48

Pharmacokinetics: 24

Diagnosis and criteria for inclusion:

Lean-to-overweight adult subjects aged between 18 and 55 years certified as generally healthy with a body mass index ≥20.0 and ≤30.0 kg/m2, fasting plasma glucose <126 mg/dL, hemoglobin A1c <6.5%, fasting triglycerides <300 mg/dL, and fasting low-density lipoprotein cholesterol <200 mg/dL at screening.

Study treatments

Investigational medicinal product(s): SAR441255

Formulation: Supplied in cartridges for parenteral administration as a sterile, nonpyrogenic, injectable, colorless solution for SC injection, containing 250 µg/mL SAR441255. The solution for injection was packaged in 3 mL cartridges. The pH of the solution was about 4.5. The solution contained the following excipients: Water for injection, glycerol (85%), methionine, metacresol, acetic acid glacial and sodium hydroxide.

Route(s) of administration: SC injection using a 0.3 mL syringe with a 0.01 mL scale and needle.

Dose regimen: Single dose SC injection administered in the morning of Day 1 in fasting condition.

Dose levels: Preliminary measured plasma levels of SAR441255 observed in subjects receiving 3, 9, and 20 µg (first 3 cohorts) suggested a much lower exposure than initially predicted, and the dose levels of Cohorts 5 and 6 were adjusted and a 7th dose cohort added to have the following dose escalation plan for SAR441255: 3, 9, 20, 40, 80, 150, and 250 µg.

Placebo:

Formulation: Sterile, clear, aqueous solution for SC injection in a vial, containing 2.15 mL. The excipients were identical to SAR441255 solution.

Route(s) of administration: SC injection using a 0.3 mL syringe with a 0.01 mL scale and needle.

Dose regimen: Identical to SAR441255

Duration of treatment: 1 day.

Duration of observation: 8 weeks.

Criteria for evaluation:

The current report is an abbreviated report, and as such, only the safety results are being presented in full. The following safety criteria were evaluated and analyzed using descriptive statistics.

Pharmacodynamics:

- Secondary
  - Glucose, insulin and C-peptide profiles before and after mixed meal

Safety:

- Primary
  - Assessment of adverse events (AEs)/treatment-emergent adverse events (TEAEs)
  - Vital signs (blood pressure and heart rate [HR] supine and standing)
  - Auricular body temperature
  - Assessment of injection site reactions
  - Clinical laboratory evaluations including hematology, biochemistry, coagulation, and urinalysis
  - Antidrug antibodies
  - Electrocardiogram intervals (HR, PR, QRS, QT, corrected QT using Fridericia's method)

Pharmacokinetics:

- Secondary
  - C_{max}, t_{max}, t_{last}, C_{trough}, AUC_{tau}, AUC (for maintenance dose only), $t_{1/2z}$, CL/F

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacodynamic sampling times:

Blood glucose, insulin, C-peptide, and glucagon

Plasma glucose (including fasting plasma glucose and postprandial plasma glucose), C-peptide, and insulin blood samples were collected on Day -1 (baseline), Day 1, and Day 2.

Determination of PD effects were analyzed by a laboratory using standardized and validated methods.

Exploratory biomarkers

Amino acids, BUN and free fatty acids samples collected for exploratory determination of PD effects were analyzed by a laboratory using standardized and validated methods. Samples were collected during the study in all cohorts.

- Amino acids, BUN: Days -1, 1 and 2
- CTX-I: Day 1 (from Cohort 5 onwards)

Pharmacokinetic sampling times:

SAR441255 concentration was measured in plasma samples collected at different timepoints during the days indicated below using specific validated bioanalytical methods. Exact timepoints were adjusted for Cohorts 5 and 6 after amended protocol 3:

- TDU15478 SAR441255 plasma samples: Days 1 until 5 (Cohorts 1 to 4), Days 1 and 2 (Cohorts 5 and 6)

Statistical methods:

Safety parameters

Safety analyses (AEs, laboratory parameters, vital signs, electrocardiograms [ECGs], etc) were based on the review of individual values, and descriptive statistics.

The safety analysis focused on the TEAE period, defined as the time from the first investigational medicinal product (IMP) administration up to the end of study visit (included).

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 22.0). Their severity was graded according National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0. The number (%) of subjects experiencing TEAEs was summarized by treatment group.

Potentially clinically significant abnormalities in clinical laboratory test results, vital signs, and ECG were flagged and summarized by treatment group using frequency tables.

Antidrug antibody status was summarized for each dose level and time window.

Pharmacokinetic parameters

Plasma SAR441255 concentrations and PK parameters were summarized for each dose and/or timepoint using descriptive statistics. Dose proportionality was assessed using a power model on C_{max} and AUC_{last} and AUC extrapolated to infinity.

Steady-state was assessed on C_{trough} using a nonlinear model. Accumulation was assessed during the first week of treatment using a linear model on log-transformed accumulation ratio. Dose proportionality was assessed using a power model on C_{max} and AUC_{last} after first and last administration of the start dose separately. Variance components of log-transformed C_{max} and AUC_{tau} were estimated using a linear model.

Summary:

Population characteristics:

A total of 48 healthy male subjects were enrolled and randomized, of which 36 subjects received SAR441255 and 12 subjects received placebo. No subject was prematurely withdrawn from the study. The majority of subjects included in the safety population were male (95.8%) and white (75.0%) and were 18 through 55 years of age (mean [SD] age: 32.1 [10.7] years). Mean (SD) body weight for subjects in the safety population at baseline was (77.38 [7.33] kg) and mean (SD) body mass index was 25.32 (2.66) kg/m^2. Demographic characteristics at baseline were similar among the placebo and SAR441255 dose groups.

Pharmacodynamic results:

The development on SAR441255 has been terminated due to Sponsor`s decision, which was not related to any safety issue. Therefore, PD results are not relevant and not presented.

Safety results:

The incidence of TEAEs was the highest in the 80 and 150 µg dose groups. In the remaining dose groups (3, 9, and 20 µg) the incidence of TEAEs was similar to placebo. No serious TEAEs, TEAEs leading to permanent discontinuation, or severe TEAEs were reported during the study.

The most frequently reported TEAEs by system organ class were gastrointestinal disorders reported for 3 of 6 subjects (nausea) who received 150 µg SAR441255 and 2 of 6 subjects (dry mouth) who received 80 µg SAR441255. Vomiting was reported for 1 of 6 subjects (16.7%) who received 150 µg SAR441255 and was considered by the Investigator to be not related to the IMP. The TEAEs of nausea were considered by the Investigator to be mild in severity and related to the IMP. All events of nausea occurred on Day 1 between 3:14 and 4:29 hours after IMP administration. Gastrointestinal disorders were less frequent in subjects who received 3 and 9 µg SAR441255 (1 of 6 subjects [16.7%]) and placebo (8.3%); in all cases the event reported was mouth ulceration. No gastrointestinal disorders were reported for subjects who received 20 and 40 µg SAR441255, respectively.

Adverse events of special interest were alanine aminotransferase increased reported for 1 of 6 subjects who received 9 µg SAR441255 and lipase increased for 1 of 6 subjects who received 3 µg SAR441255.

Except for 1 AESI of lipase increased rated as Grade 2, all AEs were graded as Grade 1 in severity and resolved without corrective treatment/therapy, except for 1 subject who had a posttreatment AE of clavicle fracture on Day 14.

At 150 µg SAR441255 mean maximum HR tended to increase above what was observed for placebo. One subject in the 150 µg reported a HR >100 bpm. There was no HR increase >120 bpm observed in any dose cohort.

There was no trend for an increase in PR, QRS, or QTc interval in any of the treatment groups.

Only 1 subject in the 20 µg dose group reported a hardly perceptible erythema; aside from this, no injection site or allergic reactions to the IMP were reported during the study as part of the AE reporting.

Pharmacokinetic results:

Following SC administration of SADs, SAR441255 was absorbed steadily and rapidly eliminated in a generally monophasic manner, with median t_{max} of 3.00 to 3.50 hours and mean $t_{1/2z}$ of 3.48 to 6.13 hours across the 20 to 150 µg range.

Median t_{last} values for SAR441255 increased with increasing dose. An apparent marginal increase in $t_{1/2z}$ with increasing dose was likely the result of more robust capture of the terminal elimination phase with increasing dose levels. The percentage of AUC calculated by extrapolation decreased with increasing dose, providing further evidence of more robust terminal phase characterization.

SAR441255 exposure (mean C_{max} and AUC) following SC of single doses increased approximately proportional to increasing dose across the 20 to 150 µg range. Where calculable, CL/F was relatively consistent across the evaluated dose range. Insufficient concentration data were available for robust C_{max} capture and AUC determination in the 3 and 9 µg dose groups. Collectively, these data were consistent with dose-independent PK of SC administered SAR441255 across the 20 to 150 µg dose range.

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